

AF/1652
Docket No.: PF-0678/US

Response Under 37 C.F.R. 1.116 - Expedited Procedure

Examining Group 1652

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yue et al.

Title: ISOLATED POLYNUCLEOTIDE ENCODING A HUMAN PSST SUBUNIT OF THE
NADH:UBIQUINONE OXIDOREDUCTASE COMPLEX (AS AMENDED)

Serial No.: 09/525,867

Filing Date: March 15, 2000

Examiner: Ramirez, D.

Group Art Unit: 1652

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Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard;
2. Brief on Appeal, including Appendix (39 pp., in triplicate); and
3. Nine (9) References (in triplicate);

The fee has been calculated as shown below.

Claims	Claims After Amendment	Claims Previously Paid For	Present Extra	Other Than Small Entity Rate	Fee	Additional Fee(s)
Total	22	24		x\$18.00		\$ 0
Indept.	3	3		x\$84.00		\$ 0
First Presentation of Multiple Dependent Claims				+280.00		\$ 0
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☒ Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c): \$ 320.00☒ Please charge Deposit Account No. 09-0108 in the amount of : \$ 320.00

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

INCYTE CORPORATION

Date: July 28, 2003Burni Dene 46,740 for

Susan K. Sather

Reg. No. 44,316

Direct Dial Telephone: (650) 845-4646

Customer No.: 27904

3160 Porter Drive

Palo Alto, California 94304

Phone: (650) 855-0555

Fax: (650) 845-4166



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By: *Diane Kizer*

Printed: Diane Kizer

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed May 27, 2003, and received by the USPTO on May 29, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the \$ 320.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting Claim 31 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Genomics, Inc. (now Incyte Corporation) (Reel 011123, Frame 0865) which is the real party in interest herein.

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(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claim 31
Claims allowed:	Claims 3-6 and 8
Claims canceled:	Claims 1-2, 7, 9, 15-22, and 24-25
Claims withdrawn:	Claims 10-14, 23, 26-30, and 32-36
Claims on Appeal:	Claim 31 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. §1.116, filed May 27, 2003, has been entered for purposes of this appeal. See the Advisory Action, mailed June 23, 2003, indicating the Amendment would be entered upon filing of an appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia*, to polynucleotides encoding polypeptides having homology to bovine PSST subunit of the NADH-ubiquinone oxidoreductase complex (g599691). These polynucleotides have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of SEQ ID NO:1 (MITP-1), for toxicology testing, and for drug discovery (see the Specification at, e.g., page 38, line 25 through page 41, line 24). As described in the Specification (e.g., Tables 1, 2, 3, and 4) the sequence of the claimed SEQ ID NO:9 polynucleotide was identified in clone 1676225 from the cDNA library BLADNOT05 derived from bladder tissue. cDNA fragments 1510924F6 (LUNGNOT14), 1676225F6 (BLADNOT05), 1676225H1 (BLADNOT05), 1988463R6 (LUNGAST01), and 3143066H1 (HNT2AZS07) were used to assemble the consensus nucleotide sequence of SEQ ID NO:9. The SEQ ID NO:1 polypeptide has 213 amino acid residues and

contains a respiratory-chain NADH dehydrogenase 20kD subunit signature sequence from V91 through E204. Electronic northern analysis of the SEQ ID NO:9 polynucleotide sequence shows expression in nervous, reproductive, and cardiovascular tissues and in tissues associated with cell proliferation and inflammation/immune.

(6) ISSUES

1. Whether the polynucleotide variants of Claim 31 meet the written description requirement of 35 U.S.C. §112, first paragraph.
2. Whether one of ordinary skill in the art would know how to make and to use the polynucleotide variants of Claim 31, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

Issue One: Rejection of Claim 31 Under 35 U.S.C. § 112, first paragraph, written description

The Examiner rejected Claim 31 under 35 U.S.C. § 112, first paragraph, alleging that the claim contains "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Final Office Action, page 3.) In particular the Examiner alleged that claimed polynucleotides comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 are not adequately described because "the genus of polynucleotides comprised by the claim is a large variable genus which can potentially encode proteins of diverse functions. The specification only discloses a single species of the genus, i.e. the polynucleotide of SEQ ID

and features of all species within the genus.” (Final Office Action, page 5.) The Examiner further states that “[t]here is no description of the mutational sites that exist in nature and there is no description of how the structure of the polynucleotide of SEQ ID NO:9 relates to the structure of any naturally-occurring variant.” (Final Office Action, page 4.)

The Examiner also contends that "function" is required for adequate written description of the claimed polynucleotides (Final Office Action, page 3 and 5, Advisory Action, pages 3-4.) Appellants submit that "function" is not required to describe and use the claimed polynucleotides disclosed in the Specification. Furthermore, the Examiner has provided neither evidence nor sound scientific reasoning to support the allegation of lack of adequate written description.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (citations omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1 and 6-7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are described, for example, at page 18, line 28 through page 19, line 15. In particular, the preferred SEQ ID NO:1 variants (at least about 80%, at least about 90%, and at least about 95% amino acid sequence identity to SEQ ID NO:1) are described, for example, at page 20, lines 29-31. In particular, SEQ ID NO:9 variants (at least about 70%, at least about 85%, and at least about 95% polynucleotide sequence identity to SEQ ID NO:9) are described, for example, at page 21, lines 4-11. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1, 3, and 4 of the Specification. Chemical and structural features of MITP-1 are described, for example, in Table 2. Given SEQ ID NO:9, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:9 at least 80% identical to SEQ ID NO:9. The Specification describes (e.g., page 11, line 22 through page 12, line 28, page 45, lines 6-9, and Table 5) how to determine whether a given sequence falls within the "at least 80% identical" scope.

There simply is no requirement that the claims recite particular polynucleotide variant sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polynucleotide variants are defined in terms of SEQ ID NO:9 ("An isolated polynucleotide selected from the group consisting of . . . b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9").

Because the recited polynucleotide variants are defined in terms of SEQ ID NO:9, the precise chemical structure of every polynucleotide variant within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

A. The present claim specifically defines the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the

recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claim at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent Claim 31 recites chemical structure to define the claimed genus:

31. An isolated polynucleotide selected from the group consisting of. . .

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9. . .

From the above it should be apparent that the claim of the subject application is fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claim is defined in terms of the chemical structure of SEQ ID NO:9. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claim. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claim of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claim of this type. By failing to base its written description inquiry "on whatever is now claimed," the Final Office Action and Advisory Action failed to provide an appropriate analysis of the present claim and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claim does not define a genus which is "large" and "variable"

Furthermore, the claim at issue do not describe a genus which could be characterized as "large" and "variable." (Final Office Action, page 5.) Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. (Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Reference No. 1). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., Reference No. 1, pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that $\geq 40\%$ identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., Reference No. 1, page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding polypeptides related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PSST subunits of the NADH:ubiquinone oxidoreductase complex and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides comprising "a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9." This variation is far less than that of all potential PSST subunits of the NADH:ubiquinone oxidoreductase complex related to SEQ ID NO:1, i.e., those PSST subunits of the NADH:ubiquinone oxidoreductase complex having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

The Examiner asserts that "nowhere in the reference [Brenner 1998, Reference No. 1] there is a suggestion that all polypeptides which share at least 30% sequence identity over 150 amino acids will share a similar function" (Advisory Action, page 8), citing as evidence Bork, van de Loo et al., Seffernick et al. and Broun et al., as well as Brenner (Trends in Genetics 15:132-133, 1999), and Witkowski et al. (Biochemistry 38: 11643-11650, 1999). The Examiner appears to be arguing that below under Issue One, Section C, Section B, although the cited references may show that functional predictions cannot be made with 100% accuracy, they

nevertheless demonstrate that a skilled artisan would believe that such predictions would be reasonably accurate. However, Brenner et al. (Reference No. 1) do provide reasonable guidelines for judging homology. Even if these guidelines are not 100% accurate, they would nevertheless lead one of skill in the art to understand that proteins meeting the thresholds of Brenner et al. would be reasonably likely to be homologous, and to share similar functions. All that is required to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, is that one of skill in the art would reasonably understand that Appellants were in possession of the claimed invention at the time the application was filed.

Moreover, the Examiner's arguments do not address the degree of variation within the claimed genus of polynucleotides. While the Examiner argues that functional assignments based on sequence homology are not 100% accurate, these arguments do not preclude the use of the thresholds of Brenner et al. to denote a reasonable degree of variation within a genus of polynucleotides or polypeptides. Brenner et al. (Reference No. 1, 1998) demonstrates that the claimed genus is not highly variant because the criteria used to define the structures of the members of the claimed genus (e.g., at least 80% identical to the polynucleotide sequence of SEQ ID NO:9) are conservative relative to the broadest criteria which a skilled artisan would consider to be reasonable (e.g., the criteria of Brenner et al. (Reference No. 1, 1998) that 30% identity over at least 150 residues, or 40% identity over at least 70 residues, reasonably denotes homology). Thus, it is proper to use the findings of Brenner et al. (1998) to demonstrate that the claimed genus of polynucleotides is not highly variant.

The Examiner states that "Brenner et al. compares amino acid sequences of functional polypeptides encoded by genes at different loci and suggests that 30% sequence identity between polypeptides having the aforementioned characteristics, i.e., functional polypeptides encoded by genes at different loci, can be used to propose functional similarity of the polypeptides." (Advisory Action, page 7.)

The SCOP database used in the Brenner et al. 1998 paper is a database of proteins with known structures. There is no information in the Brenner et al. 1998 paper about whether the polypeptides are "at different loci" and the Brenner et al. 1998 paper does not use the term "different loci." In the Brenner et al. 1998 paper the SCOP database was used to test the reliability of sequence comparison methods. The Brenner et al. 1998 paper does not discuss

predicting "functional similarity", but rather evolutionary relationships. Use of this database of proteins with known structures allowed the authors to determine whether homologies predicted from the sequence comparison methods tested in the article were truly similar structurally. The Brenner et al. 1998 paper is not trying to predict relationships between proteins; the Brenner et al. 1998 paper is evaluating known methods of predicting protein relationships. One cannot test the ability of sequence comparison methods in predicting actual structural homology if one starts with protein sequences whose structures were not already known previously and independently of the sequence comparison.

The Brenner et al. 1998 paper results are based on the SCOP database as a test set. The relationships among the SCOP proteins are already known based on non-sequence comparison methods. The structures and functions of the SCOP proteins do not need to be ascertained from sequence comparison methods. The Brenner et al. 1998 paper results allow one to generalize to the much more common situation of NOT KNOWING the structural and functional relationships between two polypeptide sequences and trying to use sequence comparison methods to predict those relationships.

If the Examiner is alleging that the "variability" of this genus is that the polypeptides encoded by the claimed polynucleotide variants have different "functions" from SEQ ID NO:1, Appellants repeat that function is immaterial to the written description of the claimed polynucleotides and their encoded polypeptides, given the description in the Specification and what is known to one of skill in the art. The written description describes polynucleotides comprising a naturally-occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9. As the claimed variants are not described by their having the same "function" as SEQ ID NO:1 or SEQ ID NO:9, the Examiner's arguments regarding "function" are not relevant to the written description issue. It is routine to calculate % identity. It is routine to use naturally-occurring polynucleotide sequences in toxicology testing. "Function" is irrelevant to the use of the claimed polynucleotide variants in toxicology testing.

The Examiner asserts that "the genus of claimed polynucleotide is related to SEQ ID NO:9, based entirely on structure (i.e. sequence), and no 3D structural analysis of PSST subunits of the NADH:ubiquinone oxidoreductase complex has been provided." (Advisory Action, page 7.) However, the rules derived by Brenner et al. (1998) are ideal for addressing a situation such

as this. Brenner et al. (1998) used the robust SCOP database to derive general rules for identifying homology between proteins, which could then be applied to any other proteins which had not been fully characterized. If it were necessary to have fully characterized a protein before it was analyzed using the standards derived by Brenner et al. (1998), then there would be no need for such analysis because the protein would already have been characterized! Thus, there is no need for an actual determination of three-dimensional structure to use the general rules of Brenner et al. (Reference No. 1, 1998).

Appellants also note that it is not necessary to determine a protein's three-dimensional structure in order to ascertain its function; there are many proteins of well-known functions whose structures have not yet been determined.

Furthermore, it is well known in the art that sequence similarity (measured by statistical scores as in the Brenner et al. 1998 paper) is predictive of similarity in functional activity. H. Hegyi and M. Gerstein ("The Relationship between Protein Structure and Function: a Comprehensive Survey with Application to the Yeast Genome," J. Mol. Biol. (1999) 288:147-164; Reference No. 2) state that "the proportion of homologues with different functions is around 10%. This shows that **there is a low chance that a single-domain protein, highly homologous to a known enzyme, has a different function.**" (Hegyi and Gerstein, Reference No. 2, page 159, column 1, emphasis added.) Furthermore, Hegyi and Gerstein in a second journal article (H. Hegyi and M. Gerstein, "Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins," Genome Research (2001) 11: 1632-1640; Reference No. 3) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3." (Hegyi and Gerstein, Reference No. 3, page 1635.) Hegyi and Gerstein also concluded that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "[t]he probability that the functions are the same in this case was 91%." (Hegyi and Gerstein, Reference No. 3, page 1636.) Hegyi and Gerstein (Reference No. 3, page 1632) further note that

Wilson et al. (2000) compared a large number of protein domains to one another in a pair-wise fashion with respect to similarities in sequence, structure, and function. Using a hybrid functional classification scheme merging the ENZYME and FlyBase systems (Gelbart et al. 1997; Bairoch 2000), they found that precise

function is not conserved below 30–40% identity, although the broad functional class is usually preserved for sequence identities as low as 20–25%, given that the sequences have the same fold. Their survey also reinforced the previously established general exponential relationship between structural and sequence similarity (Chothia and Lesk 1986).

Therefore, it is well known in the art that sequence identity can be used to reliably predict functional similarity.

C. The references cited by the Examiner are not relevant to the instant claim

Based on the references of Bork (Genome Research, 10:398–400, 2000) van de Loo et al. (Proc. Natl. Acad. Sci. U.S.A. 92:6743–6747, 1995) Seffernick et al. (2001; J. Bacteriol. 183:2405–2410), and Broun et al. (Science 282:1315–1317, 1998), the Examiner suggests that “[t]he genus of polynucleotides comprised by the claim is a large variable genus which can potentially encode proteins of diverse function” and that “[t]he specification discloses only discloses a single species of the claimed genus, i.e. the polynucleotide of SEQ ID NO:9, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus” (Final Office Action, page 5). The Examiner in the Advisory Action again cites Bork, van de Loo et al., Seffernick et al. and Broun et al., as well as Brenner (Trends in Genetics 15:132–133, 1999), and Witkowski et al. (Biochemistry 38: 11643–11650, 1999), alleging that “it is unclear as to how one of skill in the art can reliably predict function with a 30% sequence identity threshold based solely on sequence homology as asserted by Applicants.” (Advisory Action, page 8.). However, Appellants respectfully disagree.

The Examiner alleges that the “state of the art teaches that sequence comparison alone should not be used to determine a protein’s function and that small amino acid changes can drastically change the function of a polypeptide.” (Final Office Action, page 4.) However, in a recent Federal Circuit decision (Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corporation and Schering Corporation; CAFC 02-1026, -1027, February 21, 2003), the Court stated that “the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence.”

The Examiner appears not to differentiate between the finding that a single amino acid substitution “may alter” the function of a polypeptide and the opinion of one of skill in the art that, more likely than not, a single amino acid substitution, or up to 20% amino acid substitutions or up to 20% nucleotide substitutions in the encoding polynucleotide, “will alter” the function of a polypeptide. The Examiner has provided no evidence that a polypeptide encoded by a polynucleotide sequence at least 80% identical to SEQ ID NO:9 would not be predicted by one of ordinary skill in the art to have the same “function” as a polypeptide encoded by SEQ ID NO:9. Furthermore, the function of the polypeptides encoded by the claimed polynucleotides is immaterial to the written description, given the description in the Specification and what is known to one of skill in the art (as discussed above).

Contrary to the assertions of the Office Action, the use of such sequence comparisons to predict protein function is supported by the Bork reference, cited by the Final Office Action and Advisory Action. The Bork reference discloses a 70% accuracy rate in bioinformatics-based predictions. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics-based predictions.

van de Loo et al. describe the cloning of a fatty acyl hydroxylase based on sequence homology between certain fatty acyl hydroxylases and fatty acyl desaturases. In this example, the authors characterize fatty acyl hydroxylases and fatty acyl desaturases as catalyzing similar reactions (e.g., van de Loo et al., page 6743, right column, last paragraph), and conclude that the reaction mechanisms of oleate 12-hydroxylase and oleate desaturase are similar based on the sequence homology between them (e.g., van de Loo et al., abstract). The Broun et al. reference relates to the same two enzymes, fatty acyl hydroxylases and fatty acyl desaturases. Since the functions of the oleate 12-hydroxylase and oleate desaturase described by van de Loo et al. and Broun et al. are similar, it is not surprising that they share 67% sequence homology.

Accordingly if Appellants had asserted that the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase, then the Examiner would have provided evidence that the assignment to this family of fatty acyl hydroxylases may be incorrect. However, Appellants did not assert the polypeptide of SEQ ID NO:1 was a fatty acyl hydroxylase or a fatty acyl desaturase. Therefore, the van de Loo et al. and Broun et al. references are irrelevant and are not scientific evidence that

the polypeptide encoded by the polynucleotide variant of SEQ ID NO:9 is not a member of the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex.

The Seffernick et al. reference describes two enzymes, a melamine deaminase and an atrazine chlorohydrolase, that are 98% identical, yet have different substrate specificities. These two enzymes belong to a class of bacterial amidohydrolases whose members are known to catalyze the hydrolytic displacement of amino groups or chlorine substituents from triazine ring compounds. Notably, the substrates of the two enzymes, melamine and atrazine, have similar structures except that melamine possesses an amino group and atrazine possesses a chlorine substituent. The two enzymes are functionally similar and catalyze hydrolytic displacement reactions as expected for this class of enzymes. Those of skill in the art, namely Seffernick et al., could readily recognize that these enzymes belonged to the class of bacterial amidohydrolases whose substrates may include s-triazine ring compounds with either amino group or chloro group substituents and assay their function accordingly. The two enzymes described by Seffernick et al. do not have "different function" as the Final Office Action implies.

Moreover, the Seffernick et al. reference is irrelevant. Appellants did not assert that the polypeptide of SEQ ID NO:1 was a bacterial aminohydrolase, and functional diversity among members of a protein family is expected to be class-specific. No evidence has been provided to support the assertion that the claimed genus of polynucleotides is "large" and "variable" and has "diverse function."

The Examiner also cites Brenner (Trends in Genetics, 15:132-133, 1999) to argue for "the unpredictability of assigning function based on structural homology." (Advisory Action, page 8.) The Examiner states that Brenner teaches "that empirical laboratory evidence is essential to know the accuracy of functional assignment (page 132, left column, second paragraph)." (Advisory Action, page 8.) The passage in Brenner that the Examiner paraphrases reads: "But how reliable are these functional assignments, upon which we depend for understanding genes and genomes? Without laboratory experiments to verify the computational methods and their expert analysis, it is impossible to know for certain." (Brenner, Trends in Genetics, page 132, left column, second paragraph.) Brenner teaches that of 340 *Mycoplasma genitalium* genes annotated by two or three groups, the error rate is at least 8%. Nowhere does Brenner teach that all functional annotation yields incorrect results or that one of ordinary skill in the art would not

find it more likely than not that the claimed polynucleotide variants at least 80% identical to SEQ ID NO:9 would encode polypeptides with the same biological function as SEQ ID NO:1.

Likewise, the Witkowski et al. reference cited by the Examiner does not provide a basis for doubting that the claimed polynucleotide variants would encode polypeptides having the same biological function as the SEQ ID NO:1 polypeptide. Witkowski et al. describe a β -ketoacyl synthase that has been converted to a malonyl decarboxylase by replacement of a critical amino acid residue. The Examiner appears to ignore the fact that both the wild-type and the Cys161Gln mutant enzyme can carry out the malonyl decarboxylase reaction (e.g., Witkowski et al., in the Abstract). Furthermore, Witkowski et al. made mutations of an amino acid residue that is known to be critical for enzyme activity. Such an example of an artificially created mutant protein would not have led a skill artisan to doubt that the claimed polynucleotide variants, which comprise naturally occurring sequences, would encode polypeptides having the biological functions of the SEQ ID NO:1 polypeptide. Moreover, Witkowski et al. state that " β -ketoacyl synthases involved in the biosynthesis of fatty acids and polyketides exhibit extensive sequence similarity and share a common reaction mechanism" (e.g., first sentence of the Abstract). This statement is evidence that one of skill in the art would reasonably conclude that the claimed polynucleotide variants would be likely to encode polypeptides having the biological functions of the SEQ ID NO:1 polypeptide.

Moreover, Appellants emphasize again that a "biological function" for the claimed polynucleotides or their encoded polypeptides is not claimed and indeed not even necessary for use of the claimed polynucleotides in toxicology testing (see, *infra*, Issue Two).

D. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written

description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 16, 1999. Much has happened in the development of recombinant DNA technology in the 19 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:9, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

E. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claim and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claim of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claim is defined in terms of the chemical structure of SEQ ID NO:9. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claim is adequately described, as evidenced by the Brenner et al. 1998 paper. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Final Office Action and Advisory Action.

For at least the above reasons, reversal of this rejection is requested.

Issue Two: Rejection of Claim 31 Under 35 U.S.C. § 112, first paragraph, enablement

The Examiner rejected Claim 31 under 35 U.S.C. §112, first paragraph, alleging that the “specification . . . does not reasonably provide enablement for a naturally-occurring polynucleotide which encodes a polypeptide of any function, wherein the polynucleotide is at least 80% sequence identical to the polynucleotide of SEQ ID NO:9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.” (Final Office Action, page 5.)

The claimed polynucleotides are enabled, i.e., they are supported by the Specification and what is well known in the art.

A. How to make

SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application (see, for example, pages 1 and 6-7 of the Sequence Listing). Variants of SEQ ID NO:1 and SEQ ID NO:9 are described, for example, on page 18, line 28 through page 19, line 15, page 20, lines 29-32, and page 21, lines 4-12. Incyte clones in which the nucleic acids encoding the human MITP-1 were first identified and libraries from which those clones were isolated are described, for example, in Tables 1, 3, and 4. Chemical and structural features of MITP-1 are described, for example, in Table 2. “Naturally occurring” polynucleotide sequences occur in nature; they are not created exclusively in a laboratory. The Specification describes how to find naturally occurring analogs and homologs in other individuals and species (e.g., page 39, lines 3-6) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the “at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9” scope (e.g., page 11, line 22 through page 12, line 32). The making of the claimed polynucleotides by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 21, lines 31-35, page 23, lines 21-25, page 24, lines 14-16, and page 34, lines 24-31. This satisfies the “how to make” requirement of 35 U.S.C. § 112, first paragraph.

The Examiner states that “the Examiner disagrees with Applicant’s contention that the specification teaches how to isolate the naturally-occurring polynucleotides encompassed by the claims wherein said polynucleotides encode PSST subunits of the NADH:ubiquinone

oxidoreductase complex.” (Advisory Action, page 11.) The Examiner further asserts that “while making the structural homologs as recited in the claim is not undue experimentation, making and testing an infinite number of these homologs and determine which ones encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, without any teaching or suggestion as to which ones are more likely to encode the protein with the desired function, is undue experimentation.” (Advisory Action, pages 11-12.)

Appellants refer the Examiner to the text of Claim 31. Claim 31 does not limit the polynucleotide variants to those “wherein said polynucleotides encode PSST subunits of the NADH:ubiquinone oxidoreductase complex.” As discussed *supra* the Specification adequately enables the making of the claimed polynucleotide variants. And indeed, the Examiner also acknowledges that “making the structural homologs as recited in the claim is not undue experimentation.” (Advisory Action, pages 11-12.)

B. How to use

Claim 31 stands rejected under 35 U.S.C. §112, first paragraph, based on the allegation that the use of the claimed polynucleotide variants is not adequately enabled. The rejection alleges in particular that “[t]he scope of the claim is not commensurate with the enablement provided in regard to the large number of naturally-occurring polynucleotides encoding proteins of different functions which have not been described and for which there is no specific use disclosed.” (Final Office Action, page 6.) The Examiner alleges that “the specification fails to provide any guidance as to how one of skill in the art can (1) determine other functions for the claimed polynucleotides, and (2) how to use those polynucleotides without undue experimentation” citing that “[t]he state of the art clearly teaches the unpredictability of determining function of structural homologs based on sequence homology.” (Final Office Action, page 6.)

The rejection of Claim 31 is improper, as the invention of that claim is enabled and has a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in human bladder tissue, as well as variants of the SEQ ID NO:9 polynucleotide

(hereinafter "the claimed polynucleotides"). The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of PSST subunits of the NADH:ubiquinone oxidoreductase complex (Specification, Table 2 and pages 1-2.) The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptides coded for by the claimed polynucleotides actually function. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants previously submitted (in unexecuted form on May 27, 2003 and in executed form on July 11, 2003) the Declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the enablement and utility of the claimed polynucleotides are without merit.

The Examiner did not consider the Bedilion Declaration, alleging that "the Examiner did not raise new issues as asserted by Applicants and the utility issues raised by the Bedilion declaration have already been presented and addressed in Paper No. 13." (Advisory Action, page 14.) Appellants note the Examiner's allegations, but do not agree.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

Persons skilled in the art would [have appreciated on March 16, 1999] that cDNA microarrays that contained the claimed polynucleotides, including the claimed Yue '867 application SEQ ID NO:9 polynucleotide variant, would be more useful tools than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating disorders of cell proliferation, inflammation, and immune response for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed polynucleotide variants can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide variants cannot be useful

without precise knowledge of their biological function. But the law has never required knowledge of biological function to prove utility and enablement. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility and enablement requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the proteins encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise function.

1. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F.2d 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

2. **Uses of the claimed polynucleotides for diagnosis of conditions and disorders characterized by expression of MITP-1, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph**

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the previously filed Bedilion Declaration and Response to Final Office Action. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

a. The uses of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the previously filed Bedilion Declaration and Response to Final Office Action. The claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility and enablement for the claimed polynucleotides.

The instant application (the Yue '867 application) claimed the benefit under 35 U.S.C. § 119(e) of provisional application United States Serial No. 60/124,655 filed on March 16, 1999 (hereinafter "the Yue '655 application"), having essentially the identical specification, with the exception of corrected typographical errors and reformatting changes. Thus page and line numbers may not match as between the Yue '867 application and the Yue '655 application. The SEQ ID NO:9 sequence recited in the Yue '867 application claims was first disclosed in the Yue '655 application and listed as SEQ ID NO:10 in the Yue '655 application. In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Yue '655 application on March 16, 1999 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, *e.g.*, ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for

evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).¹

In connection with his explanations, Dr. Bedilion states that the “specification of the Yue ‘655 application would have led a person skilled in the art on March 16, 1999 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of disorders of cell proliferation, inflammation, and immune response to conclude that a cDNA microarray that contained the claimed polynucleotides, including the claimed Yue ‘867 application SEQ ID NO:9 polynucleotide variant, would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the claimed polynucleotides, including the claimed Yue ‘867 application SEQ ID NO:9 polynucleotide variant.” (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, “[p]ersons skilled in the art would [have appreciated on March 16, 1999] that cDNA microarrays that contained the claimed polynucleotides, including the claimed Yue ‘867 application SEQ ID NO:9 polynucleotide variant, would be more useful tools than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating disorders of cell proliferation, inflammation, and immune response for such purposes as evaluating their efficacy and toxicity. “ *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-March 16, 1999 publications showing the state of the art on March 16, 1999 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion’s explanations in paragraph 15 of his Declaration include more than three pages of text and six subparts ((a)-(f)), he specifically states that his explanations are not “all-inclusive.” *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on March 16, 1999 (and for several years prior to March 16, 1999) “without any doubt” appreciated that the toxicity (or lack of toxicity) of any proposed drug was

¹Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Yue ‘655 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

“one of the most important criteria to be evaluated in connection with the development of the drug” and how the teachings of the Yue ‘655 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Yue ‘655 application at the time it was filed “would have wanted their cDNA microarray to have a [claimed polynucleotide, including the SEQ ID NO:9 variant] probe . . . because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to March 16, 1999.” (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Yue ‘655 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities and adequate uses for the claimed polynucleotides.

Nowhere does the Patent Examiner address the fact that, as described on page 41, lines 14-24 and page 48, line 18 through page 49, line 2 of the instant application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 (“Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)” (emphasis added)).

The Bedilion Declaration shows that a number of pre-March 16, 1999 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Yue '655 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published before or shortly after the filing of the Yue '655 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.

* * *

Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

* * *

Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal

. . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis in original.)

John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 4):

In a pre-March 16, 1999 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Reference No. 5). (emphasis added.)

b. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, e.g., John C. Rockett et al., (Reference No. 4, *supra*):

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug

candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 4, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 6); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 7).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip. (Reference No. 6, page 156.)

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Reference No. 8, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 9), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

c. The similarity of the polypeptides encoded by the claimed polynucleotide variants to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility and enablement of the use of the claimed polynucleotide variants can be imputed based on the relationship between the polypeptides they encode and another polypeptide of unquestioned utility, the SEQ ID NO:1 polypeptide. The polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the

art would recognize more than a reasonable probability that the polypeptide encoded by the claimed invention has utility similar to the SEQ ID NO:1 polypeptide. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the claimed polynucleotide variants are at least 80% identical to SEQ ID NO:9 over the entire length of SEQ ID NO:9. This is more than enough homology to demonstrate a reasonable probability that the utility of polypeptide encoded by SEQ ID NO:9 can be imputed to the claimed polynucleotide variants (through the polypeptides they encode). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et al., Reference No. 1, *supra*.)

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Most important, none contradicts the Brenner et al. 1998 paper's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Based on the references of Bork (Genome Research, 10:398-400, 2000) van de Loo et al. (Proc. Natl. Acad. Sci. U.S.A. 92:6743-6747, 1995) Seffernick et al. (2001; J. Bacteriol. 183:2405-2410), and Broun et al. (Science 282:1315-1317, 1998), the Examiner suggests that "[t]he state of the art clearly teaches the unpredictability of determining function of structural homologs based on sequence homology." (Final Office Action, page 6). The Examiner in the Advisory Action also cites Brenner (Trends in Genetics 15:132-133, 1999), and Witkowski et al. (Biochemistry 38: 11643-11650, 1999) in support of these arguments. However, Appellants respectfully disagree. (See *supra*, Issue One, Written Description.)

The Examiner must accept Appellants' demonstration that the homology between the claimed polynucleotide variants and the SEQ ID NO:9 polynucleotide demonstrates a use by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt this use. See *In re Langer*, 503

F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

d. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequences of the claimed polynucleotides and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotides and its use of those polynucleotides on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

3. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating enablement and utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established uses for the claimed polynucleotides are not enabled. (Final Office Action at pages 5-10.) The Examiner is incorrect both as a matter of law and as a matter of fact.

a. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Enablement and Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological "function" of the claimed invention, the claimed invention's enablement is not adequate. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person

of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of enablement. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

b. Membership in a Class of Useful Products Can Be Proof of Enablement and Utility

Despite the uncontradicted evidence that the claimed polynucleotides encodes polypeptides in the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides, the Examiner refused to impute the utility of the members of the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides to the polypeptides encoded by the claimed polynucleotides.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial

likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses the polypeptides encoded by the claimed polynucleotides as if the general classes in which they are included are not the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides does not. The family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that the polypeptides encoded by the claimed polynucleotides would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of PSST subunits of the NADH:ubiquinone oxidoreductase and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the polypeptides encoded by the claimed polynucleotides are useful. It follows that the claimed polynucleotides also are useful.

- c. Because the uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.**

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotides themselves, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays and chromosomal mapping (Specification, page 38, line 25 through page 42, line 16).

d. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility and Enablement of the Claimed Invention: Biological function, disease association, and differential expression are irrelevant to enablement of the use of the claimed polynucleotides

The Examiner states that "the specification fails to disclose the specific diseases, conditions and/or biological processes associated with the expression of naturally-occurring polynucleotides encoding proteins of any function encompassed by the claim" and "the specification fails to disclose which are the expression levels associated with a particular disease/condition or which mutations in the claimed polynucleotides are indicative of a disease and/or condition," and therefore "it is unclear how the claimed polynucleotides can be used as disease markers or as target for drug discovery or toxicology testing." (Final Office Action, page 9, emphasis in original.)

Appellants have demonstrated a utility for the claimed polynucleotides irrespective of whether or not a person would wish to perform additional experimentation on biological function or associated "biological processes" as another utility. The fact that additional experimentation could be performed to determine the functionality of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides does not preclude, and is in fact irrelevant to, the actual utility of the invention. That utility exists today regardless of the specific function of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The Examiner confuses use with function.

Appellants need not demonstrate whether the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides, are differentially expressed or associated with any disease, only whether the claimed polynucleotides or their encoded polypeptides are useful. The claimed polynucleotides and the polypeptides encoded by the claimed polynucleotides are useful whether or not the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are differentially expressed or associated with any disease.

The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. Monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polynucleotide or polypeptide, regardless of the differential expression or disease association of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides. The claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides are useful for measuring the toxicity of drug candidates specifically targeted to other polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides.

Appellants note that monitoring the expression of the claimed polynucleotides or the polypeptides encoded by the claimed polynucleotides is a method of testing the toxicology of drug candidates during the drug development process. If the expression of a particular polynucleotide or polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound may have undesirable toxic side effects that may limit its usefulness as a specific drug. Toxicology testing using cDNA microarrays reduces time needed for drug development by weeding out compounds which are not specific to the drug target. Learning this from a cDNA microarray in a protein expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide or polypeptide whose expression is being monitored.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any *reasons* why one would doubt that the guidance provided by the present Specification would enable one to make and use the naturally-occurring sequences at least 80% identical to SEQ ID NO:9. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:9.

(9) CONCLUSION

Appellants request that the rejections of the claim on appeal be reversed for at least the reasons above.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: July 28, 2003

Bruni Brune Reg. No. 46,740 for

Susan K. Sather

Reg. No. 44,316

Direct Dial Telephone: (650) 845-4646

Customer No.: 27904

3160 Porter Drive

Palo Alto, California 94304

Phone: (650) 855-0555

Fax: (650) 849-8886

Enclosures:

1. Steven E. Brenner et al. Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. U.S.A. 95:6073-6078 (1998) (previously submitted also with the Response to Final Office Action)
2. H. Hegyi and M. Gerstein, The Relationship between Protein Structure and Function: a Comprehensive Survey with Application to the Yeast Genome, J. Mol. Biol. (1999) 288:147-164
3. H. Hegyi and M. Gerstein, Annotation Transfer for Genomics: Measuring Functional Divergence in Multi-Domain Proteins, Genome Research (2001) 11: 1632-1640
4. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (previously submitted also with the Response to Final Office Action)
5. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (August 1997) (previously submitted also with the Response to Final Office Action)

6. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (previously submitted also with the Response to Final Office Action)
7. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (previously submitted also with the Response to Final Office Action)
8. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (previously submitted also with the Response to Final Office Action)
9. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (previously submitted also with the Response to Final Office Action)

APPENDIX - CLAIMS ON APPEAL

31. (As Once Amended) An isolated polynucleotide selected from the group consisting of:

- a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:9,
- b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO:9 over the entire length of SEQ ID NO:9,
- c) a polynucleotide completely complementary to a polynucleotide of a),
- d) a polynucleotide completely complementary to a polynucleotide of b), and
- e) an RNA equivalent of a)-d).